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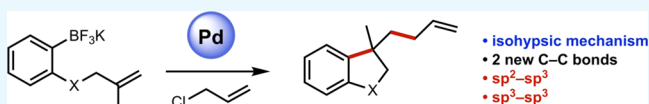
Synthesis of 3,3-Disubstituted Heterocycles by Pd-Catalyzed Arylallylation of Unactivated Alkenes

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Supporting Information

ABSTRACT: Finding new methods of carbon–carbon bond formation is a key goal in expanding current methodology for heterocycle formation. Because of their inherently nonplanar shape, new methods of forming sp^3 -rich scaffolds are of particular importance. Although there are methods for combining heterocyclization and formation of new sp^3 – sp^3 carbon–carbon bonds, these form the carbon–heteroatom bond rather than a carbon–carbon bond of the heterocycle. Here, we show a new alkene arylallylation reaction that generates a heterocycle with concomitant formation of two new carbon–carbon bonds. Furthermore, we demonstrate that this process occurs through an isohypsic (redox neutral) mechanism. Overall, this carboallylation reaction gives a new route to the synthesis of 3,3-disubstituted heterocycles.



1. INTRODUCTION

Heterocycles are found in a vast array of biologically active molecules and complex natural products. Consequently, many synthetic strategies have evolved to access these motifs.¹ Palladium-catalyzed methods are among the most widely used, due to the versatility and functional group tolerance of these cycles.² Most Pd-catalyzed heterocycle forming reactions take advantage of the nucleophilicity of the heteroatom as a key feature of the overall process. For example, we have previously shown that difunctionalisation of alkenes by heteroallylation can be used to generate a range of O- and N-containing heterocycles (Figure 1a).³ A lesser-used set of reactions utilizes starting materials where the carbon–heteroatom bonds are already in place.⁴ For example, Pd-promoted cyclization of aryl bromide 3, followed by Sonogashira-type coupling affords oxindole 4 (Figure 1b).⁵

The inclusion of more sp^3 -hybridized carbons in medicinal chemistry programmes has been shown to correlate to increased clinical success.⁶ As a complement to our earlier alkene heteroallylation work that generates heterocycles substituted with a new $C(sp^3)$ – $C(sp^3)$ bond at the 2 position (Figure 1a), we became interested in developing a Pd-catalyzed synthesis of 3,3-disubstituted heterocycles with accompanying $C(sp^3)$ – $C(sp^3)$ bond formation (Figure 1c). The success of this transformation would provide a new potential strategy to access complex biologically active compounds, such as the nM norepinephrine reuptake inhibitor daledalin, or the neurokinin receptor antagonist 7 (Figure 2).⁷

A single literature report describes Pd-catalyzed heterocycle synthesis from aryl boronic acids (8 → 9, Scheme 1).⁸ This process likely proceeds through a Pd(0)–Pd(II) catalytic cycle, including β -hydride elimination and reoxidation of the Pd by oxygen. On the basis of this precedent as well as our experience on developing an isohypsic (redox neutral) heteroallylation of alkenes (Figure 1a), we set out to develop an alkene

carboallylation reaction that would generate 3,3-disubstituted heterocycles with concomitant sp^3 – sp^3 C–C bond formation (Figure 1c).

2. RESULTS AND DISCUSSION

2.1. Optimization. An initial attempt at carboallylation was carried out using conditions similar to the heteroallylation (Table 1). Pleasingly, this resulted in formation of the desired dihydrobenzofuran 11, albeit as a minor component, with the main products being that of direct allylation 12 and deboronation 13 (entry 1). A change of the allyl halide from bromide to chloride resulted in decreased formation of the deboronation product 13 (entry 2). Lowering the number of the equivalents of allyl chloride caused an improvement in the ratio of 11:12, although the formation of 13 was also increased (entries 3 and 4). Continuing with 2 equivalents of allyl chloride, the effect of the catalyst system was examined (Table 2). The use of phosphine ligands proved detrimental, with none of the desired product formed (entries 2 and 3). Palladium(II) catalyst $PdCl_2$ led to the slightly decreased formation of the desired product, along with lower formation of deboronation product 13 (entry 4), whereas palladium(0) catalysts did not result in formation of the desired product (entries 5–7). The use of phosphonite catalyst 14⁹ resulted in an improved ratio between the desired and direct coupling products, but use of this catalyst was discontinued because of the formation of several additional unidentified side products (entry 8).

Moving from an aqueous base to a solid base greatly improved the ratio between 11:12 (Table 3, entries 1 and 2). Use of other solid bases, such as sodium hydroxide or cesium

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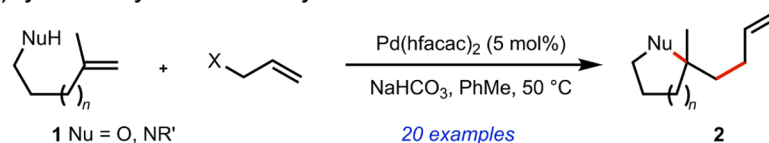
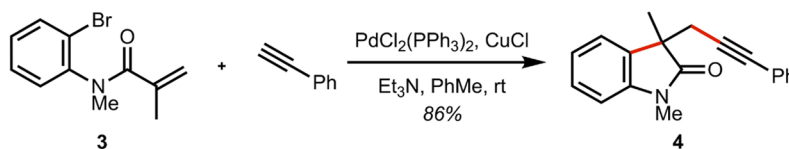
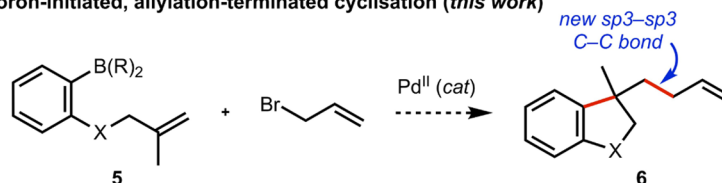
(a) cyclisation by alkene heteroallylation³(b) halide-initiated cyclisation⁵(c) boron-initiated, allylation-terminated cyclisation (*this work*)

Figure 1. Examples of Pd-catalyzed heterocycle formation and our plan for a new synthesis of 3,3-disubstituted heterocycles.

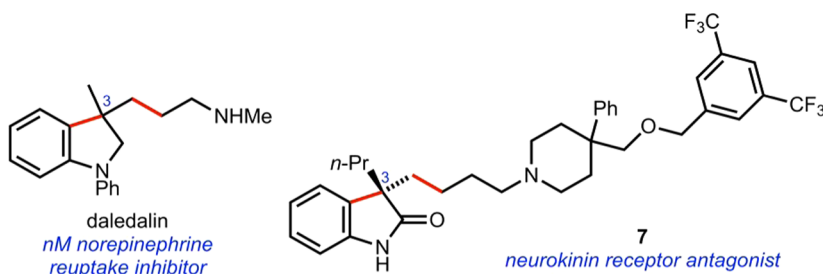
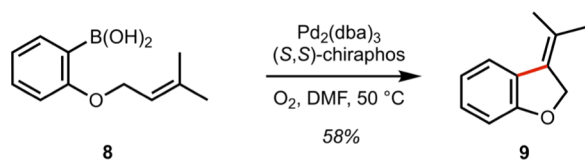


Figure 2. Biologically active 3,3-disubstituted heterocycles.

Scheme 1. Heterocyclization of Boronic Acid 8



fluoride, caused lower or zero conversion to the desired product (entries 3 and 4). Use of organic bases, such as triethylamine, also resulted in formation of the desired product as a minor component (entry 5).

Next, the choice of solvent was examined (Table 4). Use of dimethylformamide (DMF) showed no conversion to the

desired product, with the only product being that of direct allylation (entry 2). Acetonitrile and tetrahydrofuran (THF) not only lowered the formation of the deboronated product but also resulted in the formation of less desired product (entries 3 and 4). Use of dimethoxyethane completely suppressed the formation of the deboronated product, although overall conversion was lowered (entry 5).

Carrying these conditions forward, the choice of boron reagent was examined (Table 5). Pinacol boronate ester proved ineffective, with only a small amount of the desired product formed, with direct allylation product **12** being the major result (entry 2). *N*-methyliminodiacetic acid (MIDA) boronate showed very low conversion, with the only product formed that of direct allylation (entry 3). Potassium

Table 1. Effect of Allyl Halide Equivalents on Product Ratios

10

(equiv.)

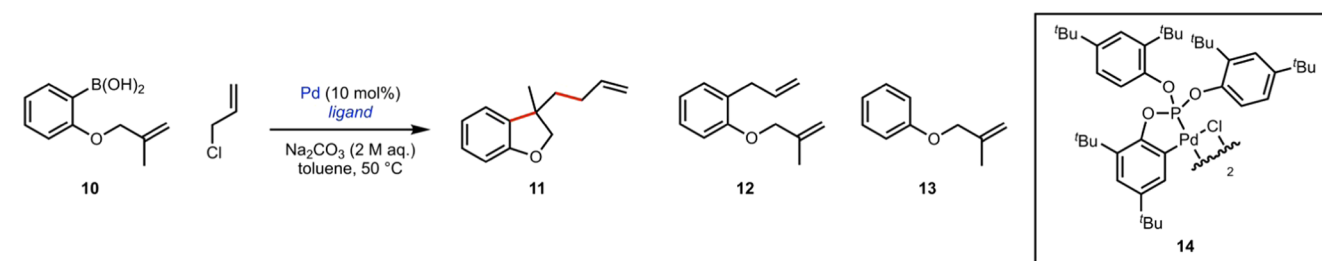
11

12

13

| entry | X | equiv. | 10 | 11 | 12 | 13 |
|-------|----|--------|-----|-----|----|-----|
| 1 | Br | 5 | 0 | 0.1 | 1 | 1.2 |
| 2 | Cl | 5 | 0.2 | 0.1 | 1 | 0.3 |
| 3 | Cl | 2 | 0.1 | 0.3 | 1 | 0.7 |
| 4 | Cl | 1.1 | 0 | 0.4 | 1 | 0.9 |

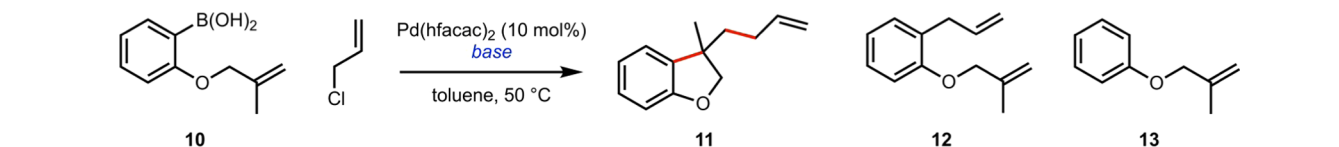
Table 2. Effect of Palladium-Catalyst System



| entry | Pd source | additive | 10 | 11 | 12 | 13 |
|----------------|----------------------------------|-----------------------------|-----|-----|----|-----|
| 1 | Pd(hfacac) ₂ | | 0.1 | 0.3 | 1 | 0.7 |
| 2 | Pd(hfacac) ₂ | PPh ₃ (1 equiv.) | 0 | 0 | 1 | 0.2 |
| 3 | Pd(hfacac) ₂ | PPh ₃ (2 equiv.) | 0.3 | 0 | 1 | 0 |
| 4 | PdCl ₂ | | 0 | 0.2 | 1 | 0.1 |
| 5 | PdCl ₂ (dppf) | | 0.3 | 0 | 1 | 0.1 |
| 6 | Pd(OAc) ₂ | | 0 | 0 | 1 | 0.2 |
| 7 | Pd ₂ dba ₃ | | 0 | 0 | 1 | 0 |
| 8 ^a | 14 | | 0 | 0.7 | 1 | 0.1 |

^aIn addition to 11 and 13, several additional side products were observed by ¹H NMR.

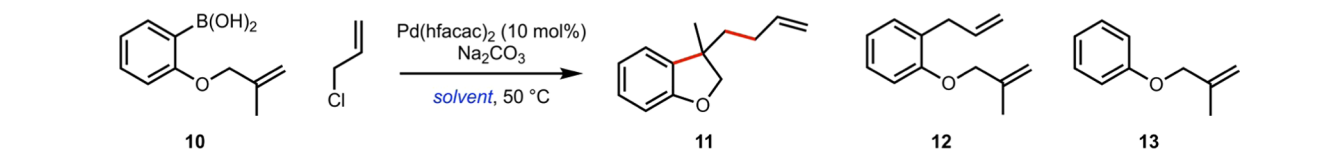
Table 3. Effect of Base



| entry | base | 10 | 11 | 12 | 13 |
|-------|--|-----|-----|----|-----|
| 1 | Na ₂ CO ₃ (2 M aq.) | 0.1 | 0.3 | 1 | 0.7 |
| 2 | Na ₂ CO ₃ ^a | 3.2 | 6.7 | 1 | 10 |
| 3 | NaOH ^a | 0 | 0.1 | 1 | 0.2 |
| 4 | CsF ^a | 0 | 0 | 1 | 0.2 |
| 5 | NEt ₃ | 0.1 | 0.3 | 1 | 3.1 |

^aBases used as solids.

Table 4. Effect of Solvent



| entry | solvent | 10 | 11 | 12 | 13 |
|-------|---------|-----|-----|----|-----|
| 1 | toluene | 3.2 | 6.7 | 1 | 10 |
| 2 | DMF | 0 | 0 | 1 | 0 |
| 3 | MeCN | 2.4 | 1.1 | 1 | 3.3 |
| 4 | THF | 3.6 | 1.4 | 1 | 0.7 |
| 5 | DME | 9.2 | 3.4 | 1 | 0 |

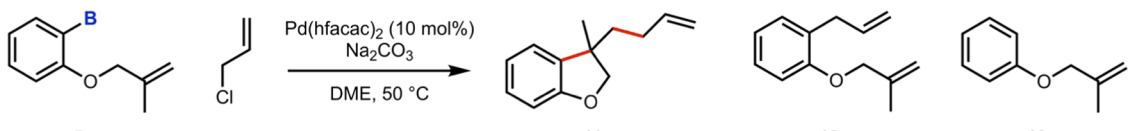
trifluoroborate 15, however, gave full conversion of the starting material while maintaining the ratio of desired/direct allylated products, forming the desired dihydrobenzofuran in 48% isolated yield (entry 4).

2.2. Reaction Scope. As the competition between desired 11 and direct coupling 12 products involves a cyclization step, the “reactive rotamer” effect¹⁰ can have an important influence on product ratio (Scheme 2). After transmetalation to form Pd(II) intermediate 16, the proximity of the *O*-methallyl chain determines how easily direct coupling or cyclization can occur. For cyclization to occur, the *O*-methallyl chain must be in close proximity to the Pd(II). As it is less sterically favorable for the

O-methallyl chain to be close to the Pd(II) (conformer 16'), it will likely spend more time at a greater distance (conformer 17). This leaves the Pd(II) intermediate 16 more vulnerable to direct coupling. By replacing the hydrogen in the 3-position with another group, orientation of the *O*-methallyl chain toward the 3-position should become less favorable. This should result in the equilibrium being displaced toward 16', therefore favoring cyclization.

To this end, the carboallylation conditions were applied to methyl-substituted potassium trifluoroborate 18 (Scheme 3). As predicted, the formation of direct allylation product 20 was greatly suppressed, with only a trace amount detected. The

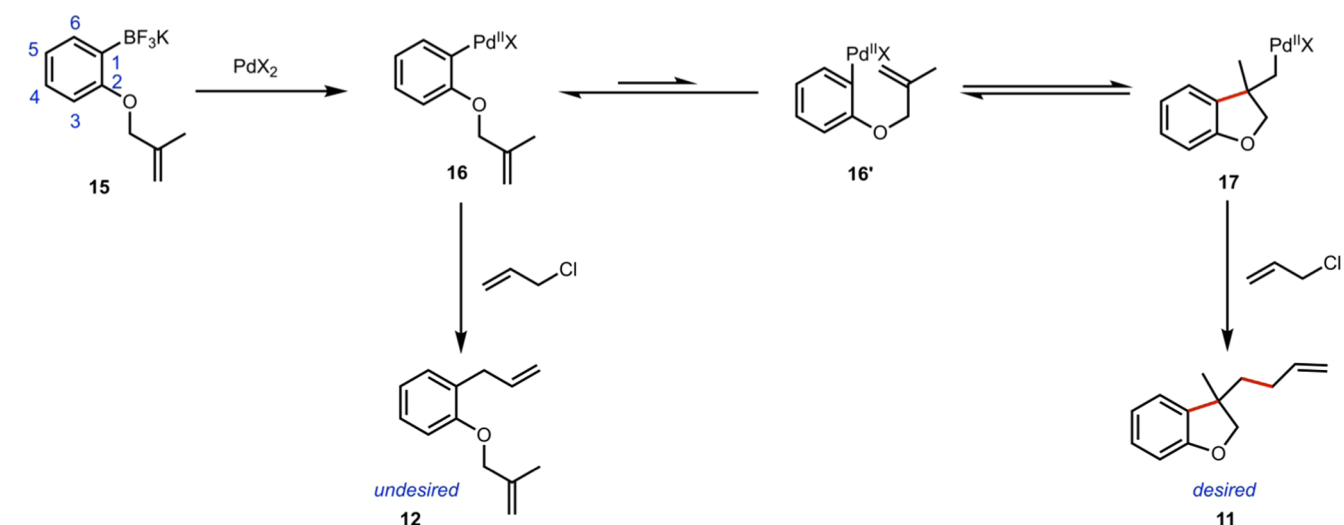
Table 5. Effect of Boronic Acid Source



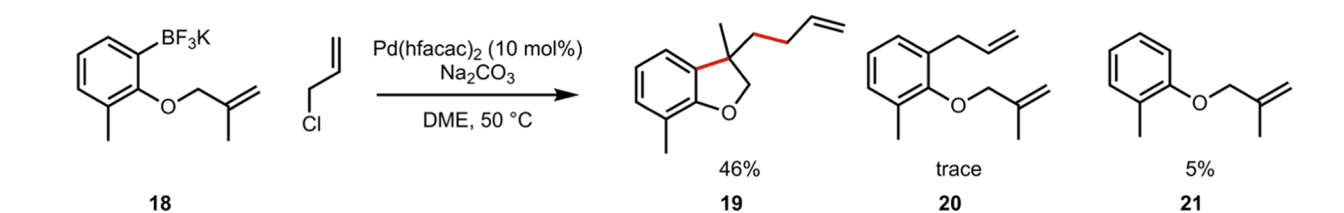
| entry | B | 10 | 11 | 12 | 13 |
|-------|--------------------|-----|------------------|----|-----|
| 1 | B(OH) ₂ | 9.2 | 3.4 | 1 | 0 |
| 2 | BPi | 0 | 0.1 | 1 | 0 |
| 3 | BMIDA | 8.8 | 0 | 1 | 0 |
| 4 | BF ₃ K | 0 | 3.5 ^a | 1 | 0.2 |

^a48% isolated yield.

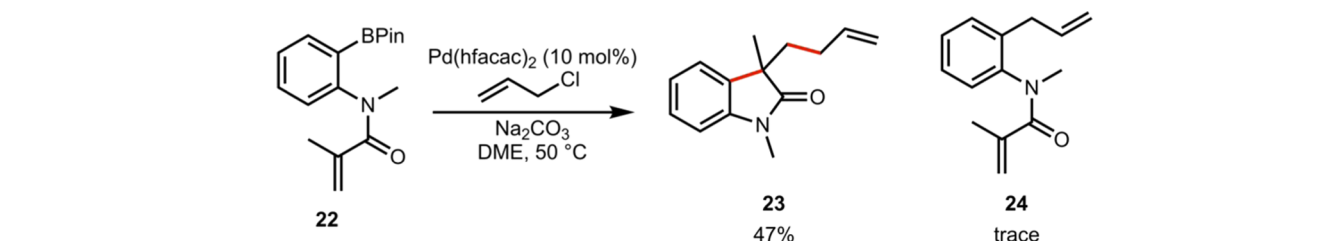
Scheme 2. Reactive Rotamer Effect on Carboallylation



Scheme 3. Carboallylation of Methyl-Substituted 18



Scheme 4. Carboallylation of Methylmethacrylamide 22



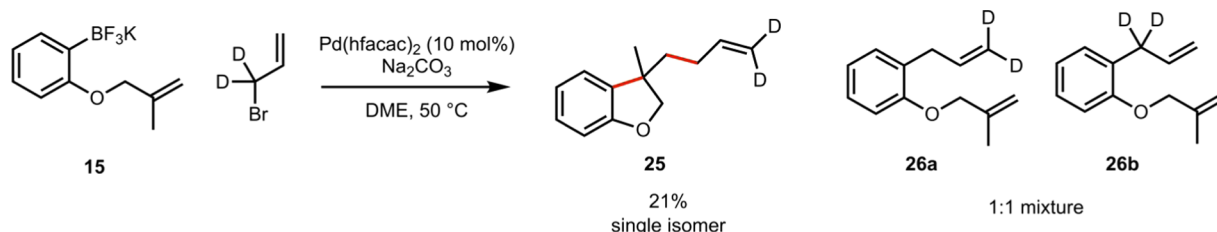
desired dihydrobenzofuran **19** was formed in 46% isolated yield.

During the development of their palladium-catalyzed cyclization of aryl halides, Zhou et al. also observed competition between cyclization and direct alkynylation.⁵ The direct alkynylation process could be largely suppressed by using *N*-methylmethacrylamides, as shown in Figure 1b. We thus employed *N*-methylmethacrylamide **22** (Scheme 4) as a

boron analog of the aryl halide substrates used by Zhou et al. Pleasingly, the carboallylation conditions were successfully resulted in formation of oxindoline **23** in 47% yield, with only trace amounts of direct allylation product **24** formed.

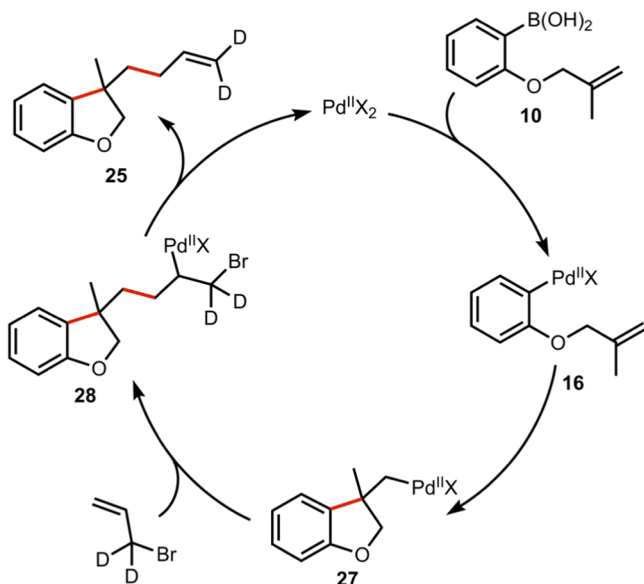
2.3. Mechanistic Study. To examine the mechanism of the arylallylation process, a deuterium-labeling study was carried out. The heterocycle formation was carried out using aryltrifluoroborate **15** using dideuteroallyl bromide (Scheme

Scheme 5. Product Distribution of Carboallylation Using Deuterium-Labeled Allyl Bromide



5). This resulted in the formation of dihydrobenzofuran **25** as a single deuterated isomer, and direct allylation products **26a** and **26b** as a 1:1 mixture of deuterated isomers (in 21 and 1% isolated yields, respectively).

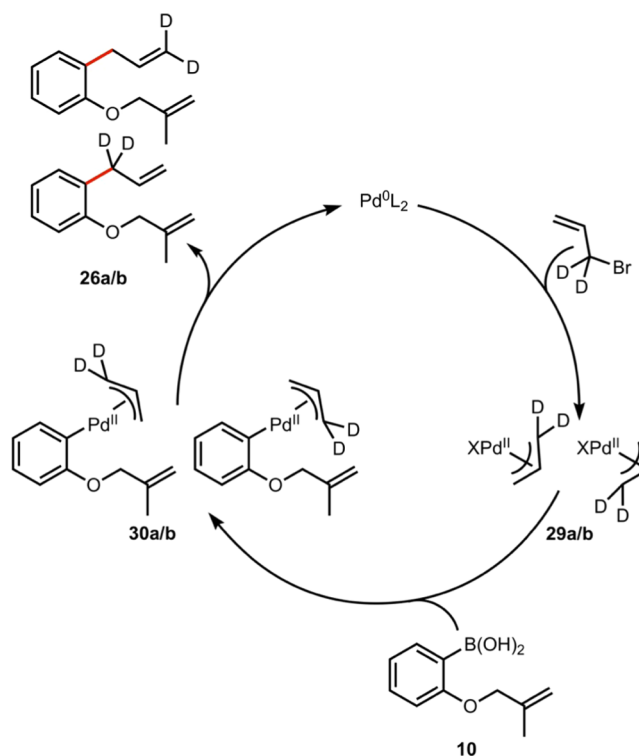
This is consistent with an isohypsic mechanism for the formation of **25** (Scheme 6). Beginning with transmetalation

Scheme 6. Proposed Mechanism for the Formation of **25**

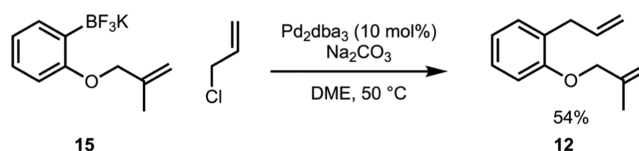
of boronic acid **10**, palladium(II) intermediate **16** is formed. Carbopalladation (olefin insertion) forms the C–C bond of the dihydrobenzofuran ring, giving **27**. A second carbopalladation can then occur, this time onto the allyl halide double bond giving palladium(II) intermediate **28**. Finally, β -halide elimination gives the dihydrobenzofuran product **25** as a single deuterated isomer, and releases the palladium(II) catalyst.

However, an isohypsic mechanism is not consistent with the formation of a 1:1 mixture of deuterated isomers of the direct allylation products **26a/b**. This suggests that the direct allylation products are formed via an alternative mechanism. Beginning with oxidative addition of palladium(0) into the allyl halide, π -allyl palladium(II) species **29a/b** are formed (Scheme 7). Transmetalation of boronic acid **10** gives rise to palladium(II) intermediates **30a/b**. Finally, reductive elimination forms the direct allylated products **26a/b** and reforms the palladium(0) catalyst.

As the dihydrobenzofuran and direct allylation products appear to be formed by separate mechanisms, it should be possible to control, which product is formed by controlling the catalyst used. Having already shown the use of a palladium(II) catalyst to form a dihydrobenzofuran product from potassium trifluoroborate **15** (Table 5, entry 4), we chose to treat **15** with

Scheme 7. Proposed Mechanism for the Formation of **26a/b**

a $\text{Pd}(0)$ catalyst. As predicted, exposure of **15** to Pd_2dba_3 and allyl chloride resulted in the sole formation of direct coupling product **12** (Scheme 8).¹¹ Interestingly, use of several common oxidants, such as benzoquinone, DDQ, O_2 , or $\text{Cu}(\text{II})$, did not favor the isohypsic cyclization process.

Scheme 8. Selective Formation of Direct Coupling Product **12**

3. CONCLUSIONS

We have developed a new Pd-catalyzed arylallylation reaction of alkenes. This reaction has been demonstrated in the formation of heterocycles, such as dihydrobenzofurans and oxindolines, results in formation of two new carbon–carbon bonds, and generates a quaternary carbon center. After elimination of the deboronation side product and suppression of the direct coupling product, the arylallylation reaction was

shown to proceed through an isohypsic palladium(II)-catalyzed mechanism. By controlling the reaction conditions, selective formation of either the cyclized or direct allylated product is possible.

4. EXPERIMENTAL SECTION

4.1. 2-(2-Methylallyloxy)phenylboronic Acid (10).

Following a literature procedure,¹² to a stirred suspension of 2-iodophenol (12 g, 52 mmol) and potassium carbonate (14 g, 110 mmol) in DMF (260 mL), was added methallyl chloride (6.1 mL, 63 mmol). The reaction mixture was heated at 70 °C for 16 h, and then cooled to room temperature (RT), diluted with EtOAc (250 mL), and the phases were separated. The organic phase was washed with water (100 mL) and brine (3 × 100 mL), dried (MgSO₄), filtered, and concentrated in vacuo to give 1-(2-methylallyloxy)-2-iodobenzene as a yellow oil (14 g, quant.). Analytical data were in accordance with literature values.¹³

Following a literature procedure,¹⁴ to a stirred solution of 1-(2-methylallyloxy)-2-iodobenzene (12 g, 43 mmol) and triisopropyl borate (12 mL, 52 mmol) in toluene/THF (4:1) (160 mL) at −78 °C, was added *n*BuLi (26 mL, 52 mmol). The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to −20 °C and quenched with 2 M aq. HCl (100 mL). The mixture was allowed to warm to room temperature and then extracted with Et₂O (2 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) gave a pale yellow solid, which was boiled in water for 2 h. After cooling, the mixture was filtered to give the title compound **10** as a pale yellow crystalline solid (4.2 g, 51%). Analytical data were in accordance with literature values.¹⁴

4.2. Potassium (2-(2-Methylallyloxy)phenyl)-trifluoroborate (15). Following a literature procedure,¹⁵ to a stirred solution of 2-(2-methylallyloxy)phenylboronic acid **10** (0.50 g, 2.6 mmol) in acetonitrile (11 mL), was added a solution of KF (0.60 g, 10 mmol) in water (1.2 mL). A solution of (L)-tartaric acid (0.80 g, 5.3 mmol) in THF (4.0 mL) was then added to the rapidly stirring solution, and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min, and then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated in vacuo to give the title compound **15** as a fluffy white solid (0.63 g, 95%).

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 7.29 (1H, dd, *J* = 7.1, 1.9 Hz, Ar-H), 6.96 (1H, ddd, *J* = 8.0, 7.2, 2.0 Hz, Ar-H), 6.66 (1H, t, *J* = 7.2 Hz, Ar-H), 6.62 (1H, d, *J* = 8.1 Hz, Ar-H), 5.16–5.14 (1H, m, C=CHa), 4.85–4.84 (1H, m, C=CHb), 4.27 (2H, s, OCH₂), 1.76 (3H, s, CH₃); ¹³C NMR (125 MHz, DMSO) δ (ppm): 161.6 (C), 142.1 (C), 138.7 (C, observed indirectly by heteronuclear multiple bond correlation (HMBC)), 133.4 (q, ³J(C-F) = 3.1 Hz, CH), 126.3 (CH), 119.1 (CH), 110.99 (CH), 110.97 (CH₂), 70.5 (CH₂), 19.3 (CH₃); IR (solid) 1597, 1437, 1209, 1188, 922 cm^{−1}; high-resolution mass spectrometry (HRMS) (ESI) exact mass calculated for C₁₀H₁₁F₃O₃ [M - K][−] *m/z* 214.0897, found *m/z* 214.0858.

4.3. Potassium (2-(2-Methylallyloxy)-3-methylphenyl)trifluoroborate (18). Following a literature procedure,¹² to a stirred suspension of 6-bromo-*o*-cresol (0.66 mL, 5.4 mmol) and potassium carbonate (1.5 g, 11 mmol) in DMF (30 mL), was added methallyl chloride (0.62 mL, 6.4

mmol). The reaction mixture was heated at 70 °C for 16 h, and then cooled to room temperature, diluted with EtOAc (30 mL), and separated. The organic phase was washed with water (20 mL) and brine (3 × 20 mL), dried (MgSO₄), filtered, and concentrated in vacuo to give 2-(2-methylallyl)-3-bromotoluene as a yellow oil (1.3 g, quant.).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.38 (1H, dd, *J* = 8.0, 1.5 Hz, Ar-H), 7.12 (1H, dq, *J* = 7.6, 0.7 Hz, Ar-H), 6.89 (1H, t, *J* = 7.8 Hz, Ar-H), 5.19–5.18 (1H, m, C=CHa), 5.02–5.01 (1H, m, C=CHb), 4.31 (2H, s, OCH₂), 2.33 (3H, s, CH₃), 1.93 (3H, d, *J* = 0.4 Hz, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 154.4 (C), 141.4 (C), 133.6 (CH), 131.2 (CH), 130.5 (C), 125.3 (CH), 117.7 (C), 113.1 (CH₂), 76.2 (CH₂), 19.9 (CH₃), 16.8 (CH₃); IR (thin film) 2920, 1653, 1464, 1452, 1260, 1220 cm^{−1}; HRMS (EI) exact mass calculated for C₁₁H₁₃OBr [M]⁺ *m/z* 240.0150, found *m/z* 240.0153.

Following a literature procedure,¹⁴ to a stirred solution of 2-(2-methylallyl)-3-bromotoluene (0.79 g, 3.3 mmol) and triisopropyl borate (0.90 mL, 3.9 mmol) in toluene/THF (4:1) (14 mL) at −78 °C was added *n*BuLi (1.8 mL, 3.9 mmol). The reaction mixture was stirred at −78 °C for 1 h, and then allowed to warm to −20 °C, and quenched with 2 M aq. HCl (10 mL). The mixture was allowed to warm to room temperature and then extracted with Et₂O (2 × 5 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave a pale yellow solid, which was boiled in water for 2 h. After cooling, the mixture was filtered to give 2-(2-methylallyloxy)-3-methyl-phenylboronic acid as a pale yellow crystalline solid (0.44 g, 66%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.68 (1H, dd, *J* = 7.2, 1.6 Hz, Ar-H), 7.31 (1H, ddt, *J* = 7.5, 1.9, 0.7 Hz, Ar-H), 7.11 (1H, t, *J* = 7.4 Hz, Ar-H), 6.04 (2H, s, B(OH)₂), 5.23 (1H, s, C=CHa), 5.05 (1H, s, C=CHb), 4.23 (2H, s, OCH₂), 2.31 (3H, s, CH₃), 1.89 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 163.1 (C), 140.9 (C), 135.1 (CH), 134.3 (CH), 130.3 (C), 124.8 (CH), 123.0 (C, observed indirectly by HMBC), 113.3 (CH₂), 78.0 (CH₂), 19.8 (CH₃), 16.1 (CH₃); IR (thin film) 3412, 2910, 1464, 1435, 1383, 1344, 1084 cm^{−1}; HRMS (CI) exact mass calculated for C₁₁H₁₅O₃ B [M]⁺ *m/z* 206.1229, found *m/z* 206.1232.

Following a literature procedure,¹⁵ to a stirred solution of 2-(2-methylallyloxy)-3-methyl-phenylboronic acid (0.072 g, 0.35 mmol) in acetonitrile (1.4 mL), was added a solution of KF (0.081 g, 1.4 mmol) in water (0.15 mL). A solution of (L)-tartaric acid (0.11 g, 0.72 mmol) in THF (0.53 mL) was then added to the rapidly stirring solution, and a white precipitate was observed immediately. The reaction mixture was stirred rapidly for 30 min, and then the precipitate was removed by filtration, and washed with acetonitrile. The filtrate was concentrated in vacuo to give the title compound **18** as a fluffy white solid (0.084 g, 89%).

¹H NMR (400 MHz, DMSO) δ (ppm): 7.20 (1H, dd, *J* = 7.2, 1.9 Hz, Ar-H), 6.87 (1H, ddd, *J* = 7.2, 2.0, 0.8 Hz, Ar-H), 6.73 (1H, t, *J* = 7.2 Hz, Ar-H), 5.05 (1H, dq, *J* = 2.4, 1.0 Hz, C=CHa), 4.83 (1H, dq, *J* = 2.7, 1.3 Hz, C=CHb), 4.23 (2H, s, OCH₂), 2.12 (3H, s, CH₃), 1.78 (3H, dd, *J* = 1.5, 0.8 Hz, CH₃); ¹³C NMR (125 MHz, DMSO) δ (ppm): 160.6 (C), 143.3 (C), 142.0 (C, observed indirectly by HMBC), 132.0 (q, ³J(C-F) = 3.0 Hz, CH), 128.3 (CH), 128.2 (C), 121.8 (CH), 110.2 (CH₂), 75.5 (CH₂), 19.6 (CH₃), 16.5 (CH₃); IR (solid)

1448, 1192, 993 cm^{-1} ; HRMS (ESI) exact mass calculated for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{OB} [\text{M} - \text{K}]^-$ m/z 228.1053, found m/z 228.1034.

4.4. *N*,2-Dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide (22). Following a modification of a literature procedure,¹⁶ a mixture of bromoaniline (0.11 mL, 1.0 mmol) and bis(pinacolato)-diboron (0.38 g, 1.5 mmol) in dioxane (4 mL) was sparged with argon for 20 min. Potassium acetate (0.20 g, 2.0 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.041 g, 0.050 mmol) were added, and the reaction mixture was stirred at 80 °C. After 24 h, bis(pinacolato)diboron (0.38 g, 1.5 mmol) was added, and the reaction mixture was stirred at 80 °C for further 24 h. After cooling to room temperature, water (10 mL) was added, and the mixture was extracted with EtOAc (3 \times 10 mL). The combined organic extracts were washed with brine, dried (MgSO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 96:4) afforded 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as an orange crystalline solid (0.15 g, 67%). Analytical data were in accordance with literature values.¹⁷

Following a literature procedure,¹⁷ to a stirred solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.10 g, 0.46 mmol) in toluene (15 mL) at 0 °C, was added triethylamine (0.50 mL, 0.46 mmol, 0.90 M) in toluene. A solution of methacryloyl chloride (0.50 mL, 0.46 mmol, 0.9 M) in toluene was added slowly (0.2 mL/min). The reaction mixture was stirred at 0 °C for 20 min and then allowed to warm to room temperature. The reaction mixture was washed with water (2 \times 20 mL), dried (MgSO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 85:15) afforded 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide as a light brown crystalline solid (90 mg, 69%). Analytical data were in accordance with literature values.¹⁷

Following a literature procedure, to a stirred suspension of 2-methyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide (0.73 g, 2.5 mmol) and potassium carbonate (0.40 g, 2.9 mmol) in DMF (41 mL), was added methyl iodide (0.22 mL, 3.6 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (100 mL) and water (100 mL), and extracted. The organic phase was washed with water (2 \times 100 mL) and brine (3 \times 100 mL), dried (MgSO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1) afforded the title compound **22** as an orange crystalline solid (0.47 g, 62%).

^1H NMR (500 MHz, $\text{DMSO}-d_6$, 80 °C) δ (ppm): 7.69 (1H, dd, J = 7.4, 1.7 Hz, Ar-H), 7.48 (1H, td, J = 7.7, 1.7 Hz, Ar-H), 7.31 (1H, td, J = 7.4, 1.1 Hz, Ar-H), 7.19 (1H, dd, J = 8.0, 1.1 Hz, Ar-H), 4.99 (2H, s, $\text{C}=\text{CH}_2$), 3.20 (3H, s, NCH_3), 1.73 (3H, s, CCH_3), 1.29 (12H, s, 4 \times CCH_3); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$, 80 °C) δ (ppm): 169.7 (C), 140.3 (C), 136.0 (C), 135.3 (CH), 132.5 (CH), 131.3 (C), 128.6 (CH), 126.2 (CH), 116.8 (CH_2), 82.9 (C), 37.7 (CH_3), 24.2 (CH_3), 19.5 (CH_3); IR (thin film) 2978, 1653, 1352, 1145 cm^{-1} ; HRMS (ESI) exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{BNNaO}_3 [\text{M} + \text{Na}]^+$ m/z 324.1741, found m/z 324.1740.

4.5. 3-(But-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran (11). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **15** (76 mg, 0.30 mmol), $\text{Pd}(\text{hfacac})_2$ (16 mg, 0.030 mmol), Na_2CO_3 (64 mg, 0.60 mmol), dimethoxyethane (1.2 mL), and allyl chloride (49 μL , 0.60 mmol), and the vial was sealed under

ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compound **11** as a colorless oil (27 mg, 48%).

^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.15–7.07 (2H, m, Ar-H), 6.88 (1H, td, J = 7.4, 1.0 Hz, Ar-H), 6.79 (1H, dt, J = 8.0, 0.5 Hz, Ar-H), 5.76 (1H, ddt, J = 16.7, 10.2, 6.4 Hz, $\text{CH}=\text{CH}_2$), 4.98 (1H, dq, J = 17.1, 1.7 Hz, $\text{CH}=\text{CHH}$), 4.94–4.90 (1H, m, $\text{CH}=\text{CHH}$), 4.37 (1H, d, J = 8.7 Hz, O-CHH), 4.16 (1H, d, J = 8.6 Hz, O-CHH), 2.15–2.05 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.92–1.82 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.73–1.68 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.36 (3H, s, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 159.9 (C), 138.5 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.7 (CH_2), 109.7 (CH), 82.6 (CH_2), 45.3 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3); IR (thin film) 2934, 1365, 1196 cm^{-1} ; HRMS (EI) exact mass calculated for $\text{C}_{13}\text{H}_{16}\text{O} [\text{M}]^+$ m/z 188.1201, found m/z 188.1203.

4.6. 3-(But-3-en-1-yl)-3-methyl-7-methyl-2,3-dihydrobenzofuran (19). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)-3-methylphenyl)-trifluoroborate **18** (220 mg, 0.80 mmol), $\text{Pd}(\text{hfacac})_2$ (42 mg, 0.080 mmol), Na_2CO_3 (170 mg, 1.6 mmol), dimethoxyethane (3.2 mL), and allyl chloride (0.13 mL, 1.6 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compound **19** as a colorless oil (74 mg, 46%).

^1H NMR (500 MHz, CDCl_3) δ (ppm): 6.96 (1H, dq, J = 7.4, 0.7 Hz, Ar-H), 6.92 (1H, dd, J = 7.4, 0.7 Hz, Ar-H), 6.80 (1H, t, J = 7.4 Hz, Ar-H), 5.75 (1H, ddt, J = 16.8, 10.2, 6.5 Hz, $\text{CH}=\text{CH}_2$), 4.99 (1H, dq, J = 17.1, 1.7 Hz, $\text{CH}=\text{CHH}$), 4.93–4.91 (1H, m, $\text{CH}=\text{CHH}$), 4.38 (1H, d, J = 8.7 Hz, O-CHH), 4.17 (1H, d, J = 8.7 Hz, O-CHH), 2.22 (3H, s, CH_3), 2.14–2.06 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.91–1.84 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.75–1.65 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.35 (3H, s, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 158.0 (C), 138.6 (CH), 134.3 (C), 129.4 (CH), 120.5 (CH), 120.4 (CH), 119.9 (C), 114.6 (CH_2), 82.4 (CH_2), 45.6 (C), 40.2 (CH_2), 29.2 (CH_2), 25.7 (CH_3), 15.2 (CH_3); IR (thin film) 2965, 2922, 1456, 1188 cm^{-1} ; HRMS (EI) exact mass calculated for $\text{C}_{14}\text{H}_{18}\text{O} [\text{M}]^+$ m/z 202.1358, found m/z 202.1357.

4.7. 3-(But-3-en-1-yl)-1,3-dimethylindolin-2-one (23).

A screw-top glass vial (4 mL) was charged with *N*,2-dimethyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-propenamide **22** (22 mg, 0.080 mmol), $\text{Pd}(\text{hfacac})_2$ (4.2 mg, 0.0080 mmol), Na_2CO_3 (17 mg, 0.16 mmol), dimethoxyethane (0.32 mL), and allyl chloride (13 μL , 0.16 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/ethyl acetate, 95:5) afforded the title compound **23** as a colorless oil (7.5 mg, 47%).

^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.27 (1H, td, J = 7.7, 1.2 Hz, Ar-H), 7.17 (1H, dd, J = 7.3, 0.7 Hz, Ar-H), 7.07 (1H, td, J = 7.5, 0.8 Hz, Ar-H), 6.84 (1H, d, J = 7.8 Hz, Ar-H), 5.68–5.60 (1H, m, $\text{CH}=\text{CH}_2$), 4.843–4.841 (1H, m, $\text{CH}=\text{CHH}$), 4.82–4.81 (1H, m, $\text{CH}=\text{CHH}$), 3.20 (3H, s, NCH_3), 2.05–2.00 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.85–1.79 (1H, m, $\text{CH}_2\text{CHHCH}=\text{CH}_2$), 1.77–1.69 (1H, m,

CHHCH₂CH=CH₂), 1.66–1.59 (1H, m, CHHCH₂CH=CH₂), 1.36 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 180.7 (C), 143.5 (C), 137.9 (CH), 134.0 (C), 127.9 (CH), 122.7 (CH), 122.6 (CH), 114.7 (CH₂), 108.0 (CH), 48.3 (CH₃), 37.7 (CH₂), 29.1 (CH₂), 26.2 (CH₃); IR (thin film) 2974, 2929, 1705, 1614, 1379, 1352 cm⁻¹; HRMS (EI) exact mass calculated for C₁₄H₁₇ON [M]⁺ *m/z* 215.1310, found *m/z* 215.1311.

4.8. 3-(4,4-Dideuteriobut-3-en-1-yl)-3-methyl-2,3-dihydrobenzofuran (25). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)-trifluoroborate **15** (64 mg, 0.25 mmol), Pd(hfacac)₂ (13 mg, 0.025 mmol), Na₂CO₃ (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL), and dideuteroallyl bromide¹⁸ (0.37 mL, 1.3 M in Et₂O, 0.50 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compound **25** as a colorless oil (8.8 mg, 19%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.13 (1H, ddd, *J* = 8.0, 7.4, 1.5 Hz, Ar-H), 7.08 (1H, ddd, *J* = 7.4, 1.5, 0.6 Hz, Ar-H), 6.88 (1H, td, *J* = 7.4, 1.0 Hz, Ar-H), 6.79 (1H, ddd, *J* = 8.0, 1.0, 0.5 Hz, Ar-H), 5.79–5.73 (1H, m, CH=CD₂), 4.38 (1H, d, *J* = 8.7 Hz, O-CHH), 4.17 (1H, d, *J* = 8.7 Hz, O-CHH), 2.15–2.06 (1H, m, CHHCH₂CH=CD₂), 1.92–1.83 (1H, m, CHHCH₂CH=CD₂), 1.73–1.69 (2H, m, CH₂CH₂CH=CD₂), 1.36 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ¹*J*(C-D) = 24.1 Hz, CD₂), 109.7 (CH), 82.6 (CH₂), 45.3 (C), 40.2 (CH₂), 29.1 (CH₂), 25.7 (CH₃); IR (thin film) 2926, 2237, 1600, 1481 cm⁻¹; HRMS (EI) exact mass calculated for C₁₃H₁₄D₂O [M]⁺ *m/z* 190.1321, found *m/z* 190.1315.

4.9. 1-(Dideuteroallyl)-2-((2-methylallyloxy)benzene (26a/b). A screw-top glass vial (4 mL) was charged with potassium (2-(2-methylallyloxy)phenyl)trifluoroborate **15** (64 mg, 0.25 mmol), Pd(hfacac)₂ (13 mg, 0.025 mmol), Na₂CO₃ (53 mg, 0.50 mmol), dimethoxyethane (1.0 mL), and dideuteroallyl bromide¹⁸ (0.37 mL, 1.3 M in Et₂O, 0.50 mmol), and the vial was sealed under ambient atmosphere. The resulting mixture was heated to 50 °C by immersion of the entire vial into a preheated aluminum block for 16 h. Purification by flash chromatography (petroleum ether/dichloromethane, 9:1) afforded the title compounds in a 1:1 mixture as a colorless oil (1 mg, 1%).

¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.19–7.14 (2H, m, Ar-H), 6.90 (1H, t, *J* = 7.4, Ar-H), 6.83 (1H, d, *J* = 8.1, Ar-H), 6.04–5.97 (1H, m, CH=CD₂/CH=CH₂), 5.11 (1H, s, OCH₂C=CHa), 5.09–5.02 (2H, m, CD₂C=CH₂), 4.98 (1H, s, OCH₂C=CHb), 4.43 (2H, s, OCH₂), 3.43 (2H, d, *J* = 6.6 Hz, CH₂C=CD₂), 1.84 (3H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 159.7 (C), 138.3 (CH), 135.0 (C), 128.2 (CH), 123.0 (CH), 120.6 (CH), 114.0 (t, ¹*J*(C-D) = 24.1 Hz, CD₂), 109.7 (CH), 82.6 (CH₂), 45.3 (C), 40.2 (CH₂), 29.1 (CH₂), 25.7 (CH₃); IR (thin film) 2926, 2237, 1600, 1481 cm⁻¹; HRMS (EI) exact mass calculated for C₁₃H₁₄D₂O [M]⁺ *m/z* 190.1321, found *m/z* 190.1315.

4.10. 2-(2-Methylallyloxy)phenylboronic acid pinacol ester. Following a modification of the reported procedure,¹⁹ a mixture of 2-(2-methylallyloxy)phenylboronic acid **10** (500 mg, 2.6 mmol) and pinacol (307 mg, 2.6 mmol) in Et₂O (15 mL) was stirred at room temperature (RT) for 17 h and then

heated at reflux for 4 h. The mixture was cooled to RT and washed with brine (3 × 25 mL). The organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The ¹H NMR spectrum of the crude material indicated approximately 80% conversion, so the residue was refluxed with pinacol (92 mg, 0.8 mmol) in Et₂O (15 mL) for 16 h. The cooled reaction mixture was washed with water (25 mL), brine (2 × 25 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to afford the title compound as a colorless oil (650 mg, 92%).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.68 (1H, dd, *J* = 7.3, 1.8 Hz, 6-H), 7.37 (1H, ddd, *J* = 8.8, 6.9, 1.4 Hz, 4-H), 6.94 (1H, td, *J* = 7.3, 0.8 Hz, 5-H), 6.84 (1H, d, *J* = 8.3 Hz, 3-H), 5.34–5.35 (1H, m, C=CHa), 4.97–4.98 (1H, m, C=CHb), 4.42 (2H, s, OCH₂), 1.86 (3H, s, CH₃), 1.35 (12H, s, 2 × C(CH₃)₂); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 163.4 (C), 141.1 (C), 136.9 (CH), 132.6 (CH), 120.4 (CH), 118.4 (C, observed indirectly by HMBC), 111.9 (CH₂), 111.6 (CH), 83.5 (2 × C), 71.6 (CH₂), 25.1 (4 × CH₃), 19.6 (CH₃); IR (thin film) 1670, 1438, 1300, 1246, 1196, 1142; HRMS (ESI) exact mass calculated for C₁₆H₂₃NaO₃B [M + Na]⁺ *m/z* 296.1669, found *m/z* 296.1664.

4.11. 2-(2-Methylallyloxy)phenylboronic Acid Methyliminodiacetic Acid Ester. Following a modification of the reported procedure,²⁰ to a solution of 2-(2-methylallyloxy)phenylboronic acid **10** (86 mg, 0.50 mmol) in DMF (1.5 mL), was added methyliminodiacetic acid (74 mg, 0.50 mmol). The resulting suspension was heated at 85 °C for 24 h and then filtered through an Isolute Si-Carbonate cartridge (500 mg), rinsing with MeCN. The filtrate was concentrated in vacuo and then partitioned between EtOAc (15 mL) and water (15 mL). The organic extracts were washed with brine (15 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc, 1:2 then 0:1) afforded the title compound as a colorless foam (100 mg, 66%).

¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.69 (1H, dd, *J* = 7.4, 3.5 Hz, 6-H), 7.34 (1H, ddd, *J* = 8.2, 7.4, 1.8 Hz, 4-H), 6.99 (1H, td, *J* = 7.3, 0.8 Hz, 5-H), 6.87 (1H, d, *J* = 8.2 Hz, 3-H), 5.02 (2H, s, C=CH₂), 4.46 (2H, s, OCH₂), 3.96 (4H, s, CH₂N(CH₃)CH₂), 2.71 (3H, s, NCH₃), 1.80 (3H, s, C(CH₃)=CH₂); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 168.0 (2 × C), 161.7 (C), 141.2 (C), 135.3 (CH), 131.5 (CH), 123.3 (C, observed indirectly by HMBC), 121.5 (CH), 114.3 (CH₂), 111.9 (CH), 72.7 (CH₂), 63.9 (2 × CH₂), 47.5 (CH₃), 19.7 (CH₃); IR (solid) 1746, 1311, 1208, 1035, 1000; HRMS (ESI) exact mass calculated for C₁₅H₁₈NNaO₅B [M + Na]⁺ *m/z* 325.1207, found *m/z* 325.1195.

4.12. 1-Allyl-2-((2-methylallyloxy)benzene (12). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.19–7.16 (2H, m, 4-H, 6-H), 6.91 (1H, td, *J* = 7.4, 1.0 Hz, 5-H), 6.85 (1H, d, *J* = 8.1 Hz, 3-H), 6.07–5.98 (1H, m, CH₂CH=CH₂), 5.13 (1H, s, C(CH₃)=CHa), 5.10–5.03 (2H, m, CH₂CH=CH₂), 4.99 (1H, s, C(CH₃)=CHb), 4.44 (2H, s, OCH₂), 3.44 (2H, d, *J* = 6.7 Hz, CH₂CH=CH₂), 1.85 (3H, s, C(CH₃)=CH₂); ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 156.4 (C), 141.2 (C), 137.2 (CH), 129.9 (CH), 129.0 (C), 127.3 (CH), 120.7 (CH), 115.5 (CH₂), 112.3 (CH₂), 111.6 (CH), 71.7 (CH₂), 34.6 (CH₂), 19.6 (CH₃); IR (thin film) 1491, 1451, 1238; HRMS (EI) exact mass calculated for C₁₃H₁₆O [M]⁺ *m/z* 188.1201, found *m/z* 188.1997.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01021.

¹H and ¹³C NMR spectra for new compounds (PDF)

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D.P. and J.F.M.H. performed the experiments. D.J.F. guided the research. All authors contributed to experimental design, data analysis, and manuscript preparation.

Notes

The authors declare no competing financial interest.

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